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Prevention of mother to child transmission of HIV in Africa

Operational research to reduce post-natal transmission and infant mortality

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Abstract
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This thesis assesses the effectiveness of the National Prevention of Mother to Child Transmission of HIV (PMTCT) programme in 3 sites in South Africa, and the quality of infant feeding counselling across four countries, Botswana, Kenya, Malawi and Uganda .

Implementation and outcome of PMTCT services were very different across the 3 sites. The Paarl site is achieving results comparable to clinical trial studies with a HIV-free survival rate of 85% at 36 weeks, while Umlazi is somewhat lower (74%) and Rietvlei, with HIV-free survival of 64%. Maternal viral load, prematurity and site were independent risk factors for infection and/or death. The regression analysis suggests that some of this difference is explained by the differences in quality of health systems across the sites. Traditional risk factors (e.g. viral load, prematurity) do not seem to explain the substantial differences in HIV-free survival between the Paarl and Rietvlei sites.

The overall mortality rate for HIV exposed infants in this cohort was 155 per 1000 live births at 36 weeks, a level higher than most other HIV exposed cohorts. The excess mortality is occurring almost completely amongst HIV infected infants who had a nine fold increased risk of mortality compared with HIV exposed but HIV negative infants. There was no significant difference in 36 week survival rates between those HIV exposed but uninfected infants and those who were not HIV exposed, Hazard ratio 0.7 (95% CI 0.3-1.5).

With respect to HIV and infant feeding most health workers across the four countries (234/334, 70%) were unable to correctly estimate the transmission risks of breastfeeding. Exposure to PMTCT training made little difference to this. Infant feeding options were mentioned in 307 out of 640 (48%) observations of PMTCT counselling session and in only 35 (5.5%) were infant feeding issues discussed in any depth; of these 19 (54.3%) were rated as poor. South Africa was similar with only two out of thirty four HIV positive mothers being asked about essential conditions for safe formula feeding before a decision was made.

This body of work has demonstrated that the gap between efficacy and effectiveness can be significant.

Keywords: HIV/AIDS, Prevention of Mother to Child Transmission of HIV, infant feeding, child health, cohort study, health systems evaluation, effectiveness

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This thesis forms part of an ongoing collaboration in HIV and infant feeding research between Uppsala University and three institutions in South Africa; the University of the Western Cape, School of Public Health; the Health Systems Trust and the Medical Research Council, Health Systems Research Unit.

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List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Jackson DJ, Chopra M, Doherty TM, Colvin MS, Levin JB, Willumsen JF, Goga AE, Moodley P; for the Good Start Study Group. Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1. AIDS 2007; 21(4):509-16.

II. Chopra M, Doherty T, Goga A, Jackson D, Persson LA. Infant mortality and risk factors amongst HIV infected, HIV exposed and HIV non-exposed infants across 3 districts in South Africa. Submitted for publication.

III. Chopra M, Dohertey T, Jackson D, Ashworth A. Preventing HIV transmission to children: quality of counselling of mothers in South Africa. Acta Paediatrica 2005; 94 (3):357-363.

IV. Chopra, M. & Rollins N. Infant feeding in the time of HIV: rapid assessment of infant feeding policy and programmes in four African countries scaling up prevention of mother to child transmission programmes. Arch Dis Child 2008; 93(4): 288-91.

Contents

Abbreviations

3TC	The anti-retroviral druglamivudine
ANC	Antenatal Care
ARV	Anti-Retroviral
CD4 count	The absolute CD4 cell count measures the number of CD4 T-cells in each cubic ml of blood
CDC	Centers for Disease Control and Prevention, Atlanta, United States of America
DHIS	District Health Information System
EBF	Exclusive Breastfeeding
EPI	Expanded Program of Immunisation
FP	Family Planning
GDP	Gross Domestic Product
HAART	Highly Active Anti-Retroviral Therapy
HIV	Human Immunodeficiency Virus
HGB	Haemoglobin
IMCI	Integrated Management of Childhood Illnesses
IMR	Infant Mortality Rate
MCH	Mother-Child Health
M&E	Monitoring and Evaluation
NGO	Non-Governmental Organization
NVT	Nevirapine
MTCT	Mother to Child Transmission of HIV
OI	Opportunistic Infections
PACTG	Paediatric AIDS Clinical Trials Group
PCP	Pneumocystis carinii pneumonia
PCR	Polymerase Chain Reaction
PMTCT	Prevention of Mother to Child Transmission
RF	Replacement Feeding
SSA	Sub-Saharan Africa
STD	Sexually Transmitted Diseases
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VCT	Voluntary Counselling and Testing
ZDV	Zidovudine
WHO	World Health Organization

Introduction

Epidemiology of mother to child transmission

By the end of 2007, an estimated 33.2 million [30.6 million – 36.1 million] people were living with HIV, of whom 2.1 million [1.9 million – 2.4 million] were children. An estimated 2.5 million [1.8 million–4.1 million] people were newly infected in 2007, and 2.1 million [1.9 million – 2.4 million] died from AIDS[1]. About two thirds of all people with HIV live in sub-Saharan Africa. Globally, an estimated 420,000 children were newly infected with HIV in 2007, mainly through mother-to-child transmission (MTCT) during pregnancy, labour/delivery and breastfeeding. Without treatment, one out of two infected infants will die before age of two[2].

For many countries in Eastern and Southern Africa (ESARO) with high burden of HIV attainment of the Millennium Development Goals (mainly Goals 4, 5 and 6) will be impossible unless there is a significant increase in the effective coverage of Prevention of Mother to Child Transmission (PMTCT) and paediatric HIV treatment programmes. The region is home to 60 per cent of all the children and 60 per cent of all pregnant women living with HIV in the world. The failure to protect women from HIV infections is mirrored in the high rate of infant infections in the region. For some countries in the region such as Botswana and South Africa HIV/AIDS is estimated to now account for more than 50% of child deaths[3].

Breastfeeding and MTCT

HIV infection can be transmitted from a mother to her child during pregnancy, peripartum or postnatally via breastfeeding. Without antiretroviral therapy or prophylaxis overall rates of MTCT range from 15 to 25% of children born to mothers who are HIV-positive and not breastfeeding, to 30 to 45% in children who are subsequently breastfed to 18 to 24 months of age[4].

Breastmilk can transmit HIV at any time during lactation; therefore the rate of HIV infection in breastfed infants is cumulative and increases with duration of breastfeeding. An individual patient meta-analysis estimated that the cumulative probability of late postnatal transmission between 4 weeks and

18 months of age was 9 infections per 100 child years of breastfeeding, and that the risk of transmission was constant throughout breastfeeding. In this meta-analysis, approximately 42% of all HIV infections in infants were attributable to breastfeeding[5].

Mechanisms and risk factors for post-natal MTCT

Despite a burgeoning literature on the possible mechanisms for the transmission of HIV through breastfeeding a recent review of the subject concluded that the exact mechanism is still unknown[6]. Possible portals of virus entry include M cells in the tonsils or overlying the intestinal lymphoid Peyer's patches, direct infection of the enterocyte or possibly direct passage through disruptions in mucosa or between immature mucosal junctions. The roles of cell-free and cell associated virus in transmission and the association between virus levels in plasma and in milk have not been reliably quantified.

Epidemiological studies have identified a number of both maternal and infant factors known to increase the risk of HIV transmission through breastmilk. The maternal factors include high plasma viral load, low CD4 count, breast pathology (including mastitis and abscesses), mode of infant feeding and prolonged duration of breastfeeding (more than 6 months)[6].

High viral loads of HIV in breastmilk are particularly important. In South Africa and Malawi[7], women with a detectable RNA viral load in their milk at any time during the first six months postpartum were more likely to transmit HIV than were women who did not have detectable virus in their milk. In West Africa, the rate of late postnatal transmission increased 2.6 times for every log10 increase in plasma RNA viral load measured in late pregnancy[8]. High maternal viral load probably also explains the finding that recent HIV infection of the mother is associated with a two fold increase in risk in breastmilk transmission[9].

Infant factors known to increase the risk of transmission through breastfeeding include damage to the mucous membranes (e.g. by oral thrush), damage to the intestinal mucosa by cow's milk or allergic reactions to complementary foods, and mixed feeding which may affect intestinal permeability[6].

HIV and child mortality/morbidity

Studies examining the causes of infant death in the context of HIV have come from either community based cohort studies or from ARV efficacy trials. A meta-analysis of community cohort studies in Kenya, Tanzania and

Malawi found that infants born to HIV-positive mothers had an almost 3-fold increased risk of death compared to infants born to HIV-negative mothers[10]. The excess risk of infant death associated with the death of a mother was 3.9. However these studies have relatively little information concerning other distal factors such as socio-economic and educational levels of mothers or more proximal biological factors related to mortality such as maternal viral load of HIV and/or infant HIV status.

The more proximal biological factors related to mortality have been identified by a recent pooled analysis of clinical studies from African trials to assess the efficacy of short course ARVs to reduce mother to child transmission of HIV[11]. This found the annual rate of death in infants who became HIV-infected was much higher than in those infants who stayed HIV-free (35.2% compared to 4.9%). In addition to infant HIV infection, mortality in this analysis was associated with geographical region, maternal death, CD4+ cell count, and timing of infection, but was not associated with ever breastfeeding or infant gender. A more recent study from Kenya[12] followed HIV-infected infants identified in order to determine predictors of mortality during the first two years of life. One of the predictors of infant mortality in addition to biological factors, such as low birth weight, was formula feeding (HR 4.0, p =0.01). All deaths amongst the non-breastfed infants occurred during the first six months of life and these infants were more likely to be of low weight for age at age one month compared to breastfed infants. These results have been important in delineating risk factors for HIV exposed infants. However they have important drawbacks with respect to informing public health decision-making.

Firstly, the clinical research study settings with their concomitant higher levels of care and service limit the generalisability of any such analysis. Secondly, there has been no analysis of the relative importance of proximal risk factors with more distal factors. In particular the role of health systems and broader socio-economic factors in influencing mortality for those affected by HIV is poorly understood but is important for planning interventions. Thirdly, the lack of a similar cohort of infants born to HIV negative mothers makes it difficult to assess the importance of maternal HIV infection on the majority of HIV negative infants born to HIV infected women.

Interventions to reduce MTCT

Drugs

Short course monotherapy regimes with either zidovudine from 36 weeks gestation, through labour and delivery, or nevirapine (NVP) given as a single

dose to the mother during labour and once to the baby reduce transmission at six weeks by as much 50%[13,14]. Although similar results have been observed with dual therapy using zidovudine and lamivudine (AZT/3TC) commencing at 36 weeks gestation, the positive effect seems to be significantly reduced after eighteen months of mixed feeding[15]. A South African study found similar short-term efficacy between single dose NVP at delivery and dual therapy with AZT/3TC administered during the intrapartum period and for seven days postpartum[16.] The World Health Organization (WHO) currently recommends the following antiretroviral regimen for preventing MTCT among women who do not have indications for antiretroviral therapy (ART) for their own health: zidovudine from 28 weeks of pregnancy; zidovudine and lamivudine plus single-dose nevirapine at the onset of labour; maternal zidovudine plus lamivudine for 7 days after delivery; and single-dose nevirapine plus one week of zidovudine for newborn infants. However in most resource constrained settings it is the short course nevirapine regime that is being used.

Reduction of transmission through safer infant feeding

Replacement feeding[1] is the only way to completely avoid post-natal HIV transmission; however, this is not an affordable, feasible, acceptable, sustainable or safe option for many HIV-infected women in developing countries. Weighed against the low (<1% per month) but ongoing risk of transmission through breast milk, breastfeeding substantially reduces the risk of infant mortality from other infectious diseases and malnutrition – by 4-6 fold in the first 6 months and close to 2 fold in the second six months of life[17]. Likewise, exclusive breastfeeding[2] provides the infant's complete nutritional needs up to the age of six months, and delays the return of maternal fertility which plays an important role in birth spacing.

Ideally randomized controlled trials should be used to guide decisions about which option to recommend (i.e. breastfeeding or replacement feeding) in a particular type of setting. Unfortunately the ethical dilemma of preventing mothers to select their choice of feeding option has limited the number of such studies. One early randomized controlled trial conducted in urban Kenya found that infants in the formula feeding group, whose mothers had access to clean water, free formula and frequent support by health workers,

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[1] *Replacement Feeding* is defined as the process of feeding a child, who is not receiving any breast milk, with a diet that provides all the nutrients the child needs.

[2] *Exclusive Breastfeeding* is defined as giving an infant no other food or drink, not even water, apart from breast milk (including expressed breast milk), with the exception of drops or syrups consisting of vitamins, mineral supplements or medicines.

had a 40% lower risk of HIV transmission but their 24 month mortality was similar to that in the breastfed group[18]. The MASHI study in Botswana[19] was a randomized controlled trial that compared the efficacy of exclusive breastfeeding plus six months of infant ZDV prophylaxis versus formula feeding plus one month of infant ZDV. Cumulative HIV transmission rates at seven months were 5.6% in the formula group and 9.0% in the breastfed plus ZDV group. The cumulative incidence of infant death by month 7 was significantly higher in the formula fed group than in the breastfed plus ZDV group (9.3% vs. 4.9%; P=0.003). However, by eighteen months there were no significant differences between the formula fed and breastfed plus ZDV group in the combined outcome HIV infection or mortality (13.9% vs. 15.1%; P=0.60).

The DITRAME PLUS study[20] conducted in Ivory Coast found a more positive outcome with formula feeding in an urban setting with high levels of support. This study found no significant difference in rates of infant illness and death at 24 months between breastfed and formula fed infants, and suggests that safe formula feeding can be achieved in settings where women have regular access to electricity, clean water, free health care, free transport to health facilities, free formula milk and formula feeding supplies.

More recently exclusive breastfeeding has been found to result in a three- to four-fold decrease in HIV transmission compared to non-exclusive breastfeeding in several large prospective studies in South Africa[21,22], Zimbabwe[23], Zambia[24] and Ivory Coast[25]. The first study to show such as association came from South Africa and found that infants who received both breastmilk and other feeds were significantly more likely to be infected by 15 months of age (36%) than those who had been exclusively breastfed for the first three months (25%) or formula fed (19%)[22]. A similar finding was reported from the ZVITAMBO trail in Zimbabwe in 2005[23]. In this study amongst 2060 HIV positive mothers with infants who were HIV-Polymerase Chain Reaction negative at 6 weeks, the rates of postnatal HIV transmission were 5.1, 6.7, and 10.5, per 100 child years of exclusive, predominant, and mixed breastfeeding respectively. Most recently the Vertical Transmission (VT) Study in KwaZulu Natal, South Africa assessed transmission rates at 6 and 22 weeks depending on feeding mode. 1372 mother-infant pairs were followed: 82% of mothers initiated exclusive breastfeeding (EBF) while women with CD4 counts <200 were most likely to use replacement feeding from birth. By 3 months two thirds of the mothers were reported to still be exclusively breastfeeding and 40% were EBF at 6 months. Replacement feeding (RF) was associated with 2-3 fold increased risk of mortality during the first 3 months compared to EBF; and mixed feeding including solids was associated with a 11 fold increased risk of infant mortality compared to EBF.

Women with CD4 counts < 200 had the highest risk of transmission, even with EBF, and of infant mortality[21].

Trials are underway to treat mothers with antiretroviral therapy during the breastfeeding period to lower their viral loads. The MASHI study in Botswana described above compared breastmilk HIV RNA and DNA in women receiving or not receiving Highly Active Antiretroviral Therapy (HAART). Results showed that women who were receiving HAART had significant reductions in breastmilk cell-free HIV RNA compared to women not receiving HAART.

A multi-country study supported by World Health Organization (WHO), known as the Kesho Bora study, is underway in four countries. The aim of the study is to assess the impact of maternal HAART on mother to child transmission and maternal health. Women with CD4+ counts < 200/mm³ or clinical AIDS will all be offered life-long HAART. Women with CD4+ counts > 500/mm³ who are at low risk of HIV transmission to infant and high risk of HAART toxicity and development of resistance will be offered short-course Mother-to-child transmission (MTCT) prophylaxis. Women with CD4+ counts 200-500/mm³ where there is a risk-benefit balance between risks of HAART, reducing MTCT and the health benefits for mothers are not known will be randomised to receive either short-course MTCT prophylaxis or triple-ARV MTCT prophylaxis during late pregnancy and breastfeeding. Given that maternal viral load is one of the most important factors in increasing the risk of HIV transmission through breastmilk, it is essential that women diagnosed with HIV during pregnancy are referred for assessment for eligibility for ARVs.

A number of trials examining the role of maternal and infant prophylaxis in reducing MTCT during breastfeeding presented some very early results at the 2008 CROI conference in Boston (www.retroconference.org). It will take a couple of years before we have the full results from these trials.

Prevention of mother to child transmission programmes across Eastern and Southern Africa

For monitoring purposes presently PMTCT programmes can be divided into two key activities: screening of pregnant women for HIV and the provision of ARV prophylaxis for the HIV positive mother and their newborn children. The most recent UNICEF/WHO/UNAIDS Update gives a summary of the most recent coverage data. Across the region the number of women being counselled for HIV has almost doubled to reach more than 3 million women.

The widespread introduction of rapid testing has markedly reduced the gap between the number of those who are counselled and those who receive test results. Coverage of HIV testing and counselling has also risen sharply from an estimated 22% to 48%. However there is a great deal of variation between countries with much of the regional increase due to improvements in countries such as Botswana, South Africa, Swaziland, Namibia, Rwanda and Kenya with over 60% coverage. By 2006 twelve countries in the region have yet to achieve 40% coverage of HIV testing and counselling for PMTCT. There has been a three-fold increase in the uptake coverage of maternal ARV for PMTCT. This rate of increase needs to be continued as there are still less than one in three HIV positive women who were receiving ARV prophylaxis in 2006. The uptake of ARV prophylaxis amongst HIV exposed infants is even more disappointing with only one in five receiving even one dose of nevaripine. Only one country in the region (Botswana) has managed to achieve more than 50% uptake coverage for mothers and infants. Quite clearly there is an urgent need to accelerate the scale up PMTCT across the region.

Challenge of scaling up PMTCT

So far HIV/AIDS programs that have reached truly national coverage have focused upon relatively simple goals, e.g. the 100% condom program in Thailand. But the scaling up of PMTCT presents greater challenges because:

- It is a complex intervention that requires co-ordination across a number of departments and partners
- The science is rapidly changing and there is still insufficient data to answer some policy questions
- It is being superimposed on a very fragile health systems suffering from chronic underfunding
- The loss of staff, especially nurses, from the public system
- It relies heavily on a robust supply system
- It can take a heavy emotional toll on health workers

However there are important insights from the scaling up of other health and nutrition programmes that can guide us. Experience suggests that programme effectiveness critically depends upon attaining sufficient coverage and intensity of the intervention[26,27]. This has implications when thinking about what needs to be scaled up. Scaling up is usually associated with increasing the geographical coverage. In addition, to ensure sufficient intensity of the intervention, other dimensions need to also be scaled up. These include: functional, organizational, and political aspects of the program[28]. All of these are pertinent to PMTCT programs.

Functional scaling up refers to the additional number and type of activities that are to be performed. In addition to the core activities of counselling, testing and medication PMTCT programs now include activities such as primary prevention and care and support, including feeding choice. This entails a scaling up of the organizational capacity and strengths. This will include resource mobilization, external partnerships, integration with other programs, capacity development etc. To achieve increasing intensity and sustainability the process of scaling up will have to include a more explicit political component. At the community level this will require the strengthening of the interaction between the formal health systems and local communities. At the national and international level it involves strengthening alliances between civil society and states to sustain pressure for resources and support.

Conducting rigorous operational research can provide important information to guide the different stakeholders as to the priorities for investments.

Operational Research for PMTCT and reduction of post-natal transmission

Although data exists from research sites on infant outcome following PMTCT interventions, there is relatively little data on maternal or infant outcomes in operational PMTCT settings in Africa[29-32]. All published data from operational settings are from cross-sectional or retrospective investigations[29,31] or where loss to follow-up was high[30,32]. Coetzee et al.[29] report a cross-sectional survey across initial PMTCT sites in Cape Town. They achieved an 81% response rate and found that 77% of mothers reporting taking the drug prophylaxis according to protocol. They report a HIV transmission rate of 8.8% at six weeks post-natal. This is almost exactly the same transmission rate (8.7%) achieved at a PMTCT programme in a teaching hospital in Johannesburg[31] and lower than the transmission rate of 10.9% reported from a site in Yaounde, Cameroon[33]. All these studies report more than 50% loss to follow up after four months. The only study of overall transmission beyond the early period is from a site in Kenya which reported an overall transmission rate of 18.1% at 14-16 weeks post-natally[34]. The authors state that this is similar to the transmission rate of 21% that was present before the introduction of the PMTCT programme. Even in research settings late post-natal transmission accounts for more than 40% of total transmission almost exclusively due to transmission through breastmilk. This highlights the importance of infant feeding counselling and support in addition to the drug and obstetric components of PMTCT.

A number of studies have documented poor quality infant feeding counselling. Even after training, health workers are often unsure of the risks of dif-

ferent feeding options. For example, an evaluation of the National Infant feeding training in South Africa[35] found low levels of knowledge amongst both participants and trainers. Most participants (88%) over-estimated the risks of breastfeeding for HIV-positive women and very few (10%) knew of the health risks of formula feeding. Similar findings have been reported in other studies throughout Africa. In the context of poor counselling, recent work in South Africa has described inappropriate choices of intended infant feeding in a cohort of HIV-positive mothers. The research noted that when women chose to formula feed was made in the absence of adequate water, fuel or disclosure of HIV status, infants were three times more likely to die or become HIV-positive by 9 months of age when compared to formula feeding in women who met all 3 criteria, suggesting that potential inappropriate choice of infant feeding method places the child at risk[36].

In contrast, evaluations of well supported sites suggest that it is possible not only to improve the quality of counselling but this can have significant impact on actual infant feeding practices such as exclusive breastfeeding[37,38]. Infant feeding counselling is thus one of the most important components of PMTCT programmes but there has been no national level evaluation of its implementation or quality.

Conceptual framework for operational research on PMTCT

Causality frameworks are diagrams that identify and illustrate the relationships among all relevant systemic, organizational, individual, or other salient factors that may influence program/project operation and the successful achievement of program or project goals. Such a framework assists in determining:

- appropriate programme elements to measure
- appropriate indicators and data
- appropriate methodology

Figure 1 provides an example of a possible framework for the assessment of PMTCT. It starts on the right with examples of the long-term goal of such programmes – the increased survival of children. In order to achieve this requires actions that will optimize the survival of all children and the reduction in the HIV incidence amongst infants. In the case of Sub-Saharan countries nearly all HIV infection in children is due to transmission from the mother to the child. Reductions in transmission can occur through the primary prevention of HIV in men and women, improvements in family planning for HIV positive women, safe obstetric practices, provision of ARVs in pregnancy and the practice of safe infant feeding after birth (i.e. the prevention of MTCT arm of the comprehensive programme).

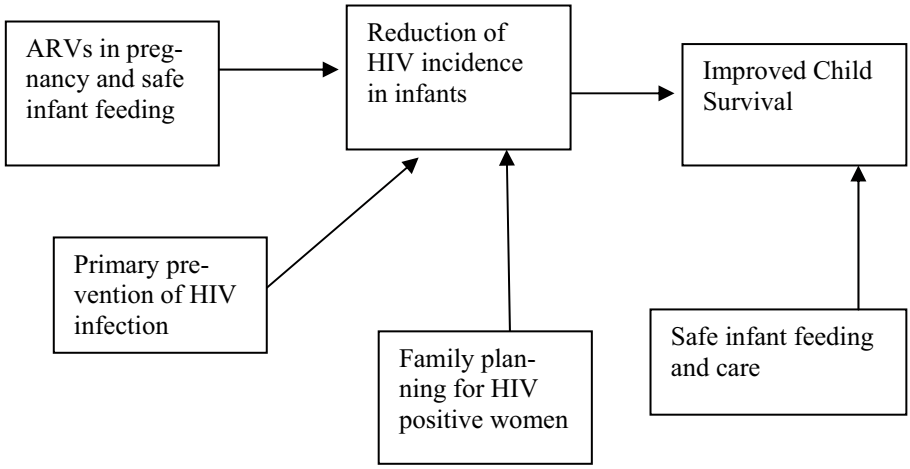


Figure 1. Framework for PMTCT assessment

In this case we are focusing only upon the prevention component of PMTCT. Central to providing an effective service is the utilization of PMTCT services. This critically depends upon community and health service factors. The main factors are outlined in figure 2 and include, inter alia increased demand for the services, availability of quality services and functioning management systems.

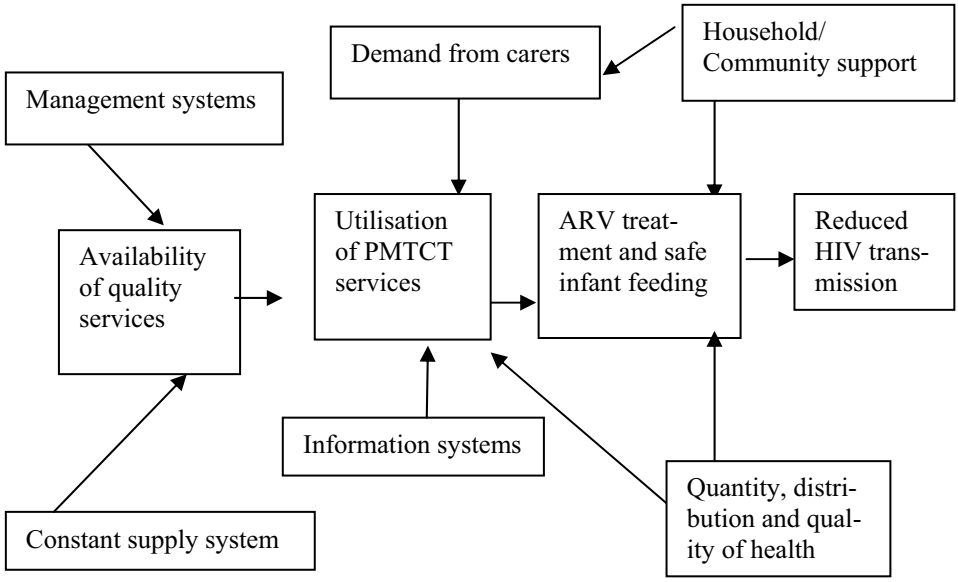


Figure 2. Inputs required for PMTCT programme

These main factors can then be further broken down into key critical activities that need to happen in order to achieve the overall aim of reduced HIV incidence in infants and hence improved child survival. This is illustrated by figure 3 and summarized below: and includes the presence of high quality VCT service, regular supplies, increased community and individual knowledge and awareness of the programme. To assess the functioning of a programme it is necessary to measure achievements in each of these result activities. For example, there is a need to measure the quality of VCT services and infant feeding counselling and the availability of HIV tests and ARV medications etc.

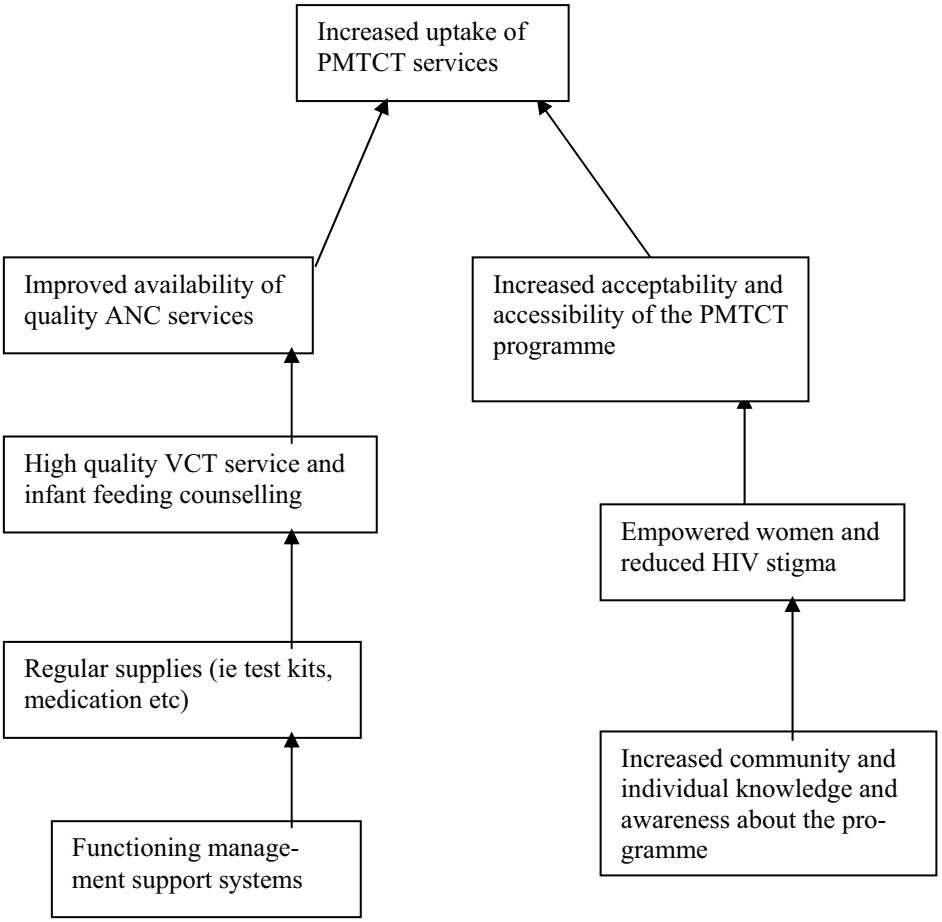


Figure 3. Critical activities for effectiveness

In summary, to be effective, a program has to fulfil the following conditions[3]:

Operational strategies and availability financial resources. Policies, planning, protocols and co-ordination between the different management levels are necessary for an operational intervention. This must be supported by adequate financial resources.

Quality of the services and human resources are major elements of the final effectiveness of the intervention. Standard procedures have to be well designed and they have to be followed. Personnel must be positive, empathetic and compassionate. The criteria for counselling quality must be met. Human resource issues include availability of trained personnel, quality of training programmes and quality of follow up after training.

Availability of key resources and management systems. An uninterrupted supply of HIV tests, ARV and laboratory supplies must be guaranteed. This requires either procurement through the usual channels of drug supply or the establishment of a parallel system (e.g. when funding for ARV is channelled through an organisation such as the Red Cross in Thailand). This in turn requires functioning management systems.

Access and continued use of service. Women have to be able to get to the place where testing, counselling and treatment by ARV is offered. For example, requesting all pregnant women to go to the district hospital outpatient ward for the first and second antenatal visit can increase the difficulty of seeking care, as the amount of travel time and cost of transportation increase. The costs for the family should not be an obstacle for women to access the intervention. Obstacles such as stigma and fear of disclosure should also be minimized. Once they have accessed the service women need to return to obtain the result of their HIV test. Then they need to go back for each of the important subsequent steps. Finally, they need to comply with their treatment. Specific strategies can be implemented to fulfil each of these critical activities.

The two studies used for this thesis used these frameworks to guide decisions regarding study design and data collection as outlined in the next section.

Study aim

The overall aim of this research was to assess the effectiveness of the routine PMTCT programme with a particular focus on reduction of late post-natal HIV transmission and infant mortality.

[3] Adapted from: Local monitoring and evaluation of the integrated prevention of mother to child HIV transmission in low-income countries. UNAIDS 2001

Specific objectives

To assess the 36 week HIV free survival of HIV exposed infants recruited through the routine PMTCT programme from three sites in South Africa. (Paper I)

To identify the risk factors for infant mortality amongst HIV exposed and unexposed infants in a cohort of infants recruited from three sites across South Africa. (Paper II)

To describe the quality of HIV and infant feeding counselling across three routine PMTCT sites in South Africa. (Paper III)

To conduct a situational assessment of infant feeding counselling and practices in the context of PMTCT programmes across four East and Southern African countries. (Paper IV)

Methods

Study designs

The research presented in this thesis arises out of two larger studies; firstly a prospective cohort study of mother to child HIV transmission (Good Start study) in South African pilot sites and secondly a multi-country evaluation of national PMTCT programmes. For the descriptive papers assessing infant feeding a cross-sectional study design was used. For the analytical papers examining the effectiveness of the PMTCT programme and risk factors for infant mortality a prospective cohort study design was used (see Table 1).

Table 1. *Summary of methods for the four papers*

	Study Design	Data collection	Main outcome indicator(s)	Main analysis
Paper I	Prospective cohort	Interviews at recruitment, 3, 24 & 36 weeks post-natal	Infant HIV negative and alive at 36 week	Cox regression
Paper II	Prospective cohort	Interviews at recruitment, 3, 24 & 36 weeks post-natal	Infant death amongst HIV exposed and HIV non-exposed infants by 36 weeks	Cox regression
Paper III	Cross-sectional	Observations	Quality & content of counselling	Descriptive statistics
Paper IV	Cross-sectional	Interviews, self-completed questionnaires & observations	Knowledge and performance of health worker	Descriptive statistics

Effectiveness of PMTCT programmes in South Africa (papers I-III)

The first three papers arise from a cohort study conducted across three government PMTCT sites in South Africa. South Africa is one of the countries worst affected by the HIV/AIDS epidemic. Annual sentinel site HIV prevalence studies in antenatal clients have been ongoing since 1990 and reveal the explosive growth of the HIV epidemic from a prevalence of less than 1% among pregnant women in 1990 to 29.5% in 2004[39]. In 6 of the country's 9 provinces at least 25% of pregnant women are now HIV positive. The package of care for the national PMTCT programme included offering all antenatal clients voluntary counselling and rapid HIV testing, infant feeding counselling, single dose nevirapine to those women identified as HIV infected, and their infants, and free formula milk for a period of 6 months for women choosing not to breastfeed. The programme also stipulated that all infants should be followed up and tested for HIV, with a rapid antibody test, at 12 months.

The importance of rigorously evaluating pilot programmes led the South African Department of Health to support a prospective cohort study of 800 mother-child pairs with active follow-up and case finding to determine the impact of the PMTCT programme on vertical transmission rates. A research consortium including the Health Systems Trust, Medical Research Council and University of the Western Cape were provided with a grant to implement this study.

The study was undertaken at three sites (Paarl, Rietvlei and Umlazi) which were among the eighteen national pilot sites. The three sites across the country were purposively chosen to reflect the differing social, economic and cultural contexts of South Africa. Paarl (Western Cape province) is a peri-urban/rural area situated in a commercial farming region. It has a relatively well functioning public health system and an antenatal HIV prevalence of 9%. Rietvlei (Eastern Cape province) is a rural area in one of the poorest regions of South Africa with a 28% antenatal HIV prevalence and a very weak health service. Umlazi (KwaZulu-Natal province), is a peri-urban township area on the outskirts of Durban with formal and informal housing and is considered to be intermediate with regard to health resources compared to the other two sites. The antenatal HIV prevalence is 47%. The study was conducted from 2002 to 2005. HIV-positive mothers were recruited from local PMTCT sites.

Study Design & Sample Size

A cohort design was selected in which regular fortnightly visits were made to both HIV positive and negative mothers to collect information on infant

feeding patterns. In addition, HIV testing of the child took place at 3 weeks, 6 months and 9 months.

Several disadvantages of the observational cohort design deserve mention. Firstly, such studies take a long time and are considerably more costly than a cross-sectional design. Secondly, they are prone to bias due to loss to follow up. Thirdly, secular changes could take place during the course of the study (i.e. changes in treatment regimen) which may not be measured. Lastly, the exposed and unexposed groups may differ in aspects other than the exposure i.e. possible confounders such as access to health services.

The sample sizes were calculated to determine overall transmission at nine months with precision ranging from +3.5% overall to +7.5% in Paarl (using estimated transmission of 18%). Recruitment over a period of 15 months yielded a total sample size of mother-baby pairs as follows: Paarl 149, Rietvlei 192, and Umlazi 324, for a total of 665.

Data Collection

All data were collected by either: A) trained field researchers using a semi-structured, or B) trained community health workers (CHWs) using structured, interviews with the mother or caregiver of the infant at the time of each visit (see Table 2 below). All interviews were in the preferred language of the subject (Xhosa, Zulu, Afrikaans or English). Community health workers were blinded to the HIV status of the mother. An initial interview was conducted by a trained field researcher at recruitment to explain the study and gain signed informed consent from each participant mother. This interview concentrated on plans for infant feeding and care of the infant, plans for disclosure of HIV status, basic knowledge of HIV/AIDS and MTCT, as well as, explaining the home visits and obtaining clear directions to the mothers' home. These interviews took approximately 30 minutes. A medical record review was also conducted on all relevant antenatal, intra-partum, post-partum, PMTCT and other records post-partum from the hospital medical record.

Home visits were made by a trained field researcher at 3 weeks, 24 weeks, and 36 weeks post-delivery. These visits took approximately 1 hour each. These visits gathered data on infant diet, cessation of breastfeeding (if applicable) at 24 and 36 weeks post-partum, influences on decisions around infant feeding choices, child care practices, socio-demographic data, participation in and satisfaction with PMTCT, health status and health visits (formal and traditional) for mother and baby, issues related to disclosure and family/social support. In addition, anthropometry measurements of infants were obtained at the 3, 24 and 36 weeks visits.

Home visits by trained CHW field staff were completed every 2 weeks until 9 weeks and then monthly thereafter until 36 weeks, except when the field researcher was visiting (i.e. CHW visits at 5,7,9,12,16,20,28,32 weeks). CHWs completed a simple structured tool on infant diet, infant health, formula availability and visits to health facilities. Mothers were also encouraged to continue participation in the PMTCT programme and to return for infant HIV testing as directed.

Table 2. *Data collection & scope of data for chohort study*

Recruitment and informed, signed consent by qualified field researcher	Either antenatally at 34-36 weeks (preferred) or after delivery, prior to discharge
Perinatal medical record review by qualified field researcher	Post-delivery - including antenatal, intra-partum, post-partum, PMTCT and any other relevant records
Semi-structured questionnaire and observation conducted by qualified field researcher (0.5 – 1 hour)	After delivery, prior to discharge 3 weeks post-delivery 24 weeks post-delivery 36 weeks post-delivery
HIV status of infants of HIV-positive mothers only (dried blood spots for DNA PCR) & Hemocue test HGB (all infants)	3 weeks post-delivery 24 weeks post-delivery 36 weeks post-delivery
Viral load of HIV-positive mothers (dried blood spots for DNA PCR) & Hemocue test HGB (all mothers)	3 weeks post-delivery 36 weeks post-delivery
Structured questionnaire conducted by local community health workers during home visits*	Fortnightly for first 9 weeks Monthly from 12 weeks to 9 months

* Umlazi did a mix of home visits and clinic visits based on the preference of the mother.

Quantifiable outcome measures included:

HIV status of the child
Infant mortality
Maternal mortality
Quality of antenatal and PMTCT care
Maternal disclosure of HIV status
Infant feeding patterns
Quality of postnatal care
Infant morbidity
Maternal morbidity
Anthropometry

Maternal Viral Loads

Qualitative outcomes were post-coded for data entry and centred on issues around decisions and influences regarding infant feeding, response to infant feeding messages and recommendations, comments on ability to carry-out recommendations, comments on health services, PMTCT programme, and disclosure of HIV status. Blood collection in infants was obtained from dried blood spots collected on Guthrie cards by means of a heel prick during home visits at 3, 24 and 36 weeks. HIV infection in infants was determined by quantitative HIV-1 RNA NASBA (Nuclisens ECL, Biomerieux) and qualitative HIV-1 DNA PCR assay (Amplicor V.1.5, Roche). Children were defined as infected with HIV-1 if they had either a detectable viral load above 10 000 copies or were positive on DNA testing.

Maternal HIV status was initially determined from routine PMTCT medical records. However, in cases where a mother recorded as being HIV positive had no detectable viral load, a repeat laboratory ELISA was done (Biomerieux Uniform 2 HIV-1 Assay followed by Biorad HIV-1 Assay). Quality control testing was performed on 5% of the samples by an independent laboratory.

For the assessment of infant feeding counselling a structured observation checklist was drawn up based upon the expected content of counselling sessions found in the training guides used by the two largest VCT training institutions. A structured questionnaire to elicit the opinion and knowledge of mothers as they left the session was also formulated. Both tools were pretested and modified before use. The two observers were experienced in conducting structured observations and were familiar with the issues regarding VCT and PMTCT. They were instructed simply to observe and not to interfere with the counselling session. Reliability was assured through the training of the observers until they had achieved over 90% inter-rater reliability for at least two joint observations consecutively between themselves. A definition list and detailed observation and interview rules were developed. Data collection sheets were collected daily after completion of fieldwork and checked. Any discrepancies were immediately discussed with the team.

Data Analysis

Quantitative data from the cohort study was entered into MS ACCESS using double data entry at a central site (MRC Durban). After validation the database was exported to Stata (v8.0) for data management and analysis. We describe the socio-demographic, medical and infant characteristics of HIV positive mothers whose infants died, HIV positive mothers whose infants did not die and HIV negative mothers using $\chi 2$ tests for categorical variables (Fisher exact test if expected cell count <5) and t-tests or Wilcoxon rank sum

tests for normally and non-normally distributed continuous variables respectively. We fitted Kaplan Meier survival curves to describe survival time in each of the 3 sites. We used Efron's method to adjust for tied survival times. In order to investigate potential risk factors for the main outcomes, we fitted Cox proportional hazards regression models to the data. For each of the hypothesized relationships we included all variables found in univariate analysis to have a p-value <0.25 into the initial Cox model; we then removed variables that were non significant in the multivariable analysis (p>0.05) and added them in one by one to determine if they were confounders of the relationship between the risk factor and the outcome. We graphically checked whether the proportional hazards assumption held for each variable in the model (using log-cumulative hazard plots).

Multi-country evaluation of PMTCT programmes (paper IV)

The final paper arises from a multi-country study for which I was the principal investigator. In recognition of the challenges of scaling up PMTCT programmes from pilot projects UNICEF initiated a review process across four countries: Botswana, Malawi, Kenya and Uganda. Most importantly, the review protocol was designed specifically to inform strategic planning processes with a health systems approach. This review protocol and tools did not aim to re-invent the many tools and assessment that have already been devised but rather to build upon them to creatively provide a framework and process by which scaling-up of PMTCT programmes can be understood, planned, implemented and sustained.

A regional workshop was held in Uganda in February 2003. UNICEF officers and senior government counterparts from five countries (Botswana, Burundi, Kenya, Malawi and Uganda) spent three days reviewing the conceptual framework (Figure 1), protocol and the indicators. The conceptual framework attempts to capture the key components necessary for the successful delivery of the treatment component of PMTCT. This review came at an opportune time for each of the five countries. Botswana has achieved national coverage with its PMTCT programme though uptake and completion of treatment remains suboptimal. Kenya and Uganda are in the process of scaling up; Malawi and Burundi are also increasing the number of PMTCT sites. Unfortunately due to the deteriorating security situation no data was collected in Burundi.

Data Capturing Tools

The Review collected data that reflected the organisational and implementation status of PMTCT programmes at national and local level and the community context within which these occur. Four modules that reflected each of these levels included a number of different data collection approaches all with the aim of trying to capture each component of the conceptual framework (Table 3).

Table 3. *Data collection tools for multi-country PMTCT evaluation*

i.	National PMTCT structures, policy and protocols	*Semi-structured interviews* with key informants (senior members of national and regional HIV/AIDS and PMTCT programmes). This module reviewed the context of PMTCT within a particular country including policy, management structures at national and regional level, programme implementation experiences to date, and budget allocations and sources of funding. It combined data from pre-existing reviews of national or other HIV programmes and focused data collection methods outside of official sources.
ii.	An audit of existing PMTCT services and other programmes	*A questionnaire* sent to all, or as many as possible, PMTCT implementation sites and to be completed by site or district managers. The audit aimed to capture information on the intensity and coverage of PMTCT programmes and to record information at different levels e.g. a single hospital and antenatal clinic, or a health district with referral hospital and feeder clinics. Quantitative information about programme implementation, primary health care services, training and staff capacity, and other information about strategic partners e.g. CBOs, NGOs and community support groups were included. The data described coverage and how scaling-up might utilise existing programmes and target areas with minimal coverage.
iii.	An in-depth assessment of PMTCT services	*Purposive sampling of at least 4 facilities* chosen by the local evaluation team. Multiple sources of information were used at sites including self-completing questionnaires by clinic staff HIV/PMTCT counsellors and health facility/site managers. Semi-structured interviews with pregnant women (exit interviews after counselling), health facility/site managers and with management staff at District level. Focus group discussion with women attending antenatal clinics and with HIV counsellors. Structured observations of HIV pre- and post test counselling and infant feeding counselling and observation of site facilities.
iv.	Community context	Key informant workshops and focus group discussions were conducted at sites where the in-depth assessment of PMTCT services were performed-

Data Collection Process

For each tool detailed standardized rules were developed. Country teams were trained individually with the same consultant spending at least one week with each team. Independent data collection teams were used in each country.

Senior policy makers and programme managers for PMTCT, child health and nutrition were interviewed using a semi-structured questionnaire. Districts offering PMTCT were selected by stratified random sampling with rural and urban strata. A total of 29 districts were randomly selected across the four countries (10 out 22 districts offering PMTCT in Botswana, 9 out of 12 in Kenya, 6 out of 9 in Malawi and 4 out of 6 in Uganda). All health facilities in the selected PMTCT districts were assessed. The facility level manager and the senior nurse in charge of maternal care were interviewed. All health workers who were identified by the facility manager as being involved in the PMTCT programme were requested to complete a self-administered questionnaire that asked questions concerning knowledge of HIV transmission risks and infant feeding. Completed questionnaires were returned by 334 (90%) health workers (27/35 in Botswana, 151/170 in Kenya, 82/85 in Malawi and 74/79 in Uganda).

Observations of PMTCT counselling sessions were also conducted at all facilities. A structured observation checklist was drawn up based upon the national training materials for counselling on infant feeding for HIV-positive mothers. This was pre-tested in each country and revised before use. Between five and seven counsellors who provided PMTCT counselling were selected per site for observation; this constituted nearly all the counsellors at the sites. Four post HIV test observations were conducted per counsellor. Reliability was assured through the training of the observers until there was over 90% inter-rater reliability for at least two joint observations consecutively between observers. Detailed observation rules and a definition list were developed. Data recording sheets were collected daily after completion of fieldwork and checked by local supervisors. Any discrepancies were immediately discussed with the field team.

In at least three sites per country focus group discussions were held with women attending ante-natal clinic and separately with men in the community. The interview guides explored general perception concerning HIV and modes of transmission. It included a specific section on HIV and breastfeeding. A total of 34 focus group discussions were conducted. Data collection occurred between July and November 2003. Ethical approval was granted by the University of the Western Cape research and ethics committee.

Quantitative data were double-entered and cleaned by the country teams and checked for completeness and consistency by an independent team based in Kenya. Quantitative data were analysed using SPSS version 11.1. Qualitative data were transcribed and analysed using a thematic approach.

Results

Significant heterogeneity in the effectiveness of routine PMTCT programmes across South Africa (Paper I)

This paper shows that the implementation, and outcome, of PMTCT services was very different across the three sites in South Africa. There were substantial differences across the three study sites with regard to maternal and infant characteristics, quality of maternity and PMTCT care, and infant feeding. Maternal socio-demographics showed significant differences for all variables, with Rietvlei being the most disadvantaged. The mean gestational age at birth was lower in Umlazi, but birthweight was similar across the sites. For antenatal and postnatal care, Rietvlei showed the poorest indicators for quality of care as measured by antenatal visits, syphilis testing, postnatal visits, and immunisation rates. With regard to infant feeding, Paarl had the lowest (36%) and Umlazi the highest (81%) proportion of infants who reported exposure to any breastmilk feedings between birth and 36 weeks of age ('ever breastfed'). For PMTCT programme indicators, Rietvlei showed the poorest performance with regard to Nevirapine per protocol, counselling, and disclosure.

The Paarl site achieved results comparable to clinical trial studies with a HIV-free survival rate of 85% at 36 weeks, while Umlazi was somewhat higher and Rietvlei, with HIV-free survival of 64%, was essentially the same as the placebo (untreated) group in the PETRA study. In the multivariable analyses the most important risk factor for HIV-transmission and/or infant death overall was maternal viral load, with an increase of 1 on the log-scale increasing the risk to the infant of HIV-transmission and/or death by about 1.5 times. Being premature also increased the risk (marginal significance in adjusted analyses p=0.058-0.093) of the infant becoming HIV-positive or dying. There was also some evidence that being 'ever breastfed' increased the risk of becoming HIV-positive or dying, although this effect was not statistically significant (p=0.13-0.16).

The regression analysis suggests that some of this difference is explained by the differences in quality of health systems across the sites. Traditional risk factors (e.g. viral load, prematurity) do not seem to explain the substantial differences in HIV-free survival between the Paarl and Rietvlei sites. The

strongest independent risk factor for HIV transmission and/or death, maternal viral load, was actually highest in the site with the best HIV-free survival, i.e. Paarl. Post-natal exposure to HIV via breastfeeding also did not account for much of the difference probably because there were high levels of mixed breastfeeding across all sites.

High mortality especially for infants with early infection (Paper II)

The overall mortality rate for HIV exposed infants in this cohort of 155 per 1000 live births at 36 weeks was higher than other HIV exposed cohorts. Coutsoudis et al. meta-analysis of seven clinical PMTCT studies from Sub-Saharan Africa estimated a cumulative mortality of 110 per 1000 live births at one year. Their estimate from the studies from South Africa was 69 per 1000 live births[5]. The high mortality is occurring in the context where the underlying infant mortality rate amongst HIV unexposed infants is much lower (37 per 1000 live births) than other parts of Africa.

The excess mortality is occurring almost completely amongst HIV infected infants who had a nine fold increased risk of mortality compared with HIV exposed but HIV negative infants. The vast majority (81.3%) of infected infants who died in this cohort had contracted early infection (i.e. were infected by 3 weeks of age) and they suffered a rapid decline in survival, with a mortality risk of 39.7% (27 out of 68 infants with early HIV infection) by 36 weeks, compared to 19.3% (6/31) for those who acquired infection after 3 weeks. The hazard ratio (HR) of mortality at 36 weeks of age in HIV-infected children compared with exposed but HIV negative children was 8.9 (95% CI 6.7-11.8). There was no significant difference in 36 week survival rates between those HIV exposed but uninfected infants and those who were not HIV exposed, Hazard ratio 0.7 (95% CI 0.3-1.5). In univariate analyses infant death amongst HIV exposed infants was strongly associated with infant positive HIV status at 3 weeks (HR 9.3 95% CI 5.6-5.4), maternal viral load greater than 100 000 (HR 4.2 (2.3-7.6), site Rietvlei compared with Paarl (HR 3.8 95% CI 1.7-8.3), inappropriate formula feeding (HR 4.5 95% CI 1.4-14.3). In a Cox regression analysis amongst HIV exposed infants the only independent risk factor for infant death was infant testing HIV-positive at three weeks of age ($p<0.003$). Other factors such as low socioeconomic score, low birth weight, four or more antenatal visits and residing in either Rietvlei or Umlazi were not associated with infant death amongst HIV exposed infants probably because of the small sample size.

Poor quality counselling especially for infant feeding (paper III)

This paper reports on the observations of PMTCT counselling sessions across all three sites. Twenty- two counsellors and a total of 60 sessions were observed and 60 exit interviews conducted. The general quality of communication skills was very good, and 73% of HIV-negative mothers were informed of the advantages of exclusive breastfeeding (EBF). However, only one of 34 HIV-positive mothers was informed about the possible side effects of nevirapine, and none was told what to do when it occurred. Only two HIV-positive mothers were asked about essential conditions for safe formula feeding before a decision about an infant feeding option was made. None of the 12 mothers choosing to breastfeed was shown how to position the baby correctly on the breast or asked whether they thought EBF was feasible. Most mothers' knowledge about infant feeding remained poor at the end of the counselling session. Half of the mothers (31/60) were planning to practice suboptimal methods of feeding, one-third (20/60) were intending to discuss their infant feeding decision with somebody. Fewer than a quarter of mothers expressed confidence in performing the actions required, and 85% could not define the term EBF.

However, two-thirds (40/60) of mothers correctly identified the dangers of mixed feeding for HIV transmission and other infections. In reply to the more open-ended questions, nearly all participants were positive about the counselling session. On further probing, a common theme was the need for more information, especially with respect to their own health and to formula feeding.

Widespread gaps in the knowledge and practice of health workers and mothers in relation to HIV and infant feeding (paper IV)

All four countries (Botswana, Kenya, Malawi and Uganda) that participated in the multi-country assessment had succeeded in training significant numbers of health workers in PMTCT. These courses were a minimum of five days in duration with an average of one day devoted to infant feeding counselling. Despite the high coverage of PMTCT training, knowledge of the actual risk of transmission from mother to child, especially postnatal transmission, was poor across all countries. Only 7% of health workers (range 4% to 20%) were correctly able to estimate the risk of transmission of HIV from an infected mother to child at birth. Less than one fifth of health workers (average 16%; range 20% to 8%) were correctly able to answer the question

‘If 100 HIV-infected women breastfeed until their children are two years old how many children will be infected at 2 years of age? (mother and child do not receive any antiretroviral medicines)’. Not only were many of the responses incorrect but in nearly all cases there was a significant over-estimate of the risks. Four of twenty-four respondents who were involved in infant feeding counselling in Botswana and seven of thirty-four in Kenya reported receiving free samples of infant formula outside of the routine PMTCT supplies. This is in direct contravention of the International Code on Breastmilk Substitutes.

Amongst lay respondents there was an almost universal belief that a HIV positive mother who breastfeeds her child will, without exception, infect the child. Exactly how this occurs was also subject to much speculation.

Discussion

Taken as a whole these papers illustrate the large gap between findings from clinical efficacy studies and actual effectiveness in operational settings. They also show the wide inequalities that can result from differences in the effectiveness of interventions. The regression analyses suggest that a mother in Rietvlei with a similar viral load, who gives birth to a similar gestational aged baby, who is fed in a similar manner as a mother in Paarl, is still more than twice as likely to experience her child becoming HIV infected or dying by nine months. The multi-country evaluation also shows widespread shortcomings in a core component of a PMTCT programme across four very highly affected countries. On a positive note the papers also show how attempting to measure and analyse the reasons for such gaps and for variations in performance can be valuable in identifying important bottlenecks for improving performance. The discussion sections of the papers discuss the particular issues related to the different findings. It is not my intention to repeat those points here, rather I will focus upon some limitations of the work and the more general health systems issues that arise from this work as a whole.

With respect to the South African study the observational study design and lack of blinding of the researchers make causal inferences and probabilistic analysis problematic. However there are plausible reasons why the difference in outcome between the sites is real. Firstly, loss to follow up was similar across the 3 sites and the characteristics of those lost to follow up were also similar. Secondly, the difference in HIV free survival across the sites is very large, so even if there was a degree of measurement bias between the sites it is unlikely to explain away such a large difference. Thirdly, the results also suggest that the wide variation in the quality of health systems is a potential explanation of the different outcomes in these two sites. Despite relatively high utilisation of health services across all sites (the mean number of ante-natal visits even in Rietvlei was >3) there were significant differences in the uptake of important programme components such as Nevirapine. The difference in quality can also be assumed from the large differences in service-related indicators such as proportion of mothers having a syphilis test, immunisation coverage and recall of counselling.

External validity is also another concern since there are only 3 sites and they were not randomly selected. Review data from across the country have also

found large variation in the provision, management and quality of the PMTCT programme[40]. Evaluation of the management of severe malnutrition in a neighbouring district to Rietvlei also found very poor outcomes that improved with external inputs but were not sustained[41]. Finally the results of early transmission from Paarl[42] are very similar to the transmission rates found across Cape Town[29] and Johannesburg[31].

The marked difference in outcomes in the three sites across South Africa despite a national protocol and training programme highlights the limitations of cost-effectiveness analysis that do not account for pre-existing weaknesses in the infrastructure and the possibility of very different outcomes. The addition of new clinical interventions, such as HIV treatment and prevention programmes, to already under-resourced and poorly functioning health systems may not lead to improved HIV-related health indicators, as these already over-burdened systems will not be able to cope with the additional work-load involved in the new programme, and may even lead to deterioration in the quality of other services. For example, Peeling et al. (Peeling, Mabey et al. 2004) found that syphilis testing and prevention remained low despite the introduction of new resources through the PMTCT programme, resulting in deaths from congenital syphilis rather than HIV.

The results from these studies suggest that the introduction of PMTCT services in disadvantaged areas with poorly functioning health services need simultaneous attention to underlying socio-economic conditions and health care infrastructure, including the provision of additional resources such as staff and funding, if the benefits of PMTCT interventions are to be shared. Most national PMTCT plans however do not account for such deficits, and the need to address inequities within the broader health care system. In South Africa, annual district health expenditure ranges from under R50 ($8) per capita to R389 ($55) per capita, with the most deprived districts with the greatest health needs, generally receiving the least resources. It is hardly surprising that PMTCT service outcomes vary so considerably given the lack of an accompanying programme of health resource redistribution. It should be noted that although controlling for health service factors such as coverage and quality made the difference in outcomes between the different sites non-significant a large amount of variability was still not accounted for. This suggests the wider socio-economic and cultural milieu is critical in explaining the variation in the final outcome of the PMTCT programme. It is not just the health sector that needs to be fixed.

While well functioning health care systems and reasonable socio-economic conditions are axiomatic to improved child health outcomes, the findings from this research also point to the on-going and vexing challenge of reducing post-natal transmission from breastfeeding. The results suggest that

breastfeeding is still a major source of mother-to-child transmission of HIV, even in the context of a PMTCT programme that offers free commercial infant formula. The final two papers highlight that infant feeding counselling and support has not received the same level of support as other parts of the PMTCT programme. In three sites in South Africa only two out of thirty four HIV positive mothers were asked about essential conditions for safe formula feeding before a decision about infant feeding was made. Interviews and observations of health workers across multiple sites in four high HIV prevalence countries also found very poor levels of technical knowledge of the risks of breastfeeding and performance of counselling. Not surprisingly there is an almost universal perception in communities that breastfeeding by HIV positive women will almost inevitable lead to the infection of the infant.

Poor infant feeding counselling is a common finding across PMTCT programmes even after training. In a report from Ndola, Zambia, in only half of observed PMTCT counselling sessions did health workers 'satisfactorily' discuss MTCT with HIV positive mothers and infant feeding options were discussed with mothers in only a third of the sessions[37]. Evaluation of training materials and training in South Africa found the technical content to be good but there were important shortcomings in terms of follow up and re-orientation of the health system. For example, there is no training or re-orientation of supervisors and doctors towards PMTCT or HIV and infant feeding. Whilst our assessment did not formally assess the training materials we did find that less than half the participants (47%) reported any follow up after the training to review practices. There was also no evidence of specific training or orientation courses for different levels of management.

Poor counselling and lack of subsequent support for the infant feeding decision almost inevitably leads to mixed feeding which may increase the risk of MTCT. There is some evidence that the introduction of PMTCT, and the provision of free formula within the programme, is being accepted by mothers who do not have the domestic conditions to safely prepare artificial feeds[43] and has led to a 'spillover' of formula feeding amongst non-HIV positive mother[44]. Successful interventions that have improved infant feeding counselling in the context of HIV have relied upon a combination of interventions apart from training: focusing upon a few appropriate options, systematic follow up after training, the use of visual tools or counselling cards, development of appropriate educational materials and spreading the counselling over several sessions[45]. Randomised trials from Brazil, Bangladesh, India and Mexico have consistently found that community based interventions such as lay counsellors also significantly increase rates of exclusive breastfeeding. There was no evidence of such strategies at health facilities or in the community being employed across PMTCT sites examined in this assessment.

More research is urgently needed on how pregnant and post-partum HIV positive women can be supported to make the most appropriate infant feeding choice for their personal circumstance and how they can be supported to implement this choice.

Scaling up PMTCT programmes

The studies that make up this thesis were conducted at the beginning of the scaling up of PMTCT programmes across southern and eastern Africa. The pertinent question to ask now is: Apart from the specific technical issues such as timing of infant HIV testing or relative importance of providing maternal HIV treatment what can these studies contribute with regards to improving the effectiveness of routine PMTCT programmes?

The introduction and spread of PMTCT in the South African sites as well as in the multi-country evaluation was done in what Carl Taylor has labelled a 'blue-print' approach[28]. In other words, experts select successful interventions from local or international experience. A blueprint is designed by outsiders with the classic features of log frameworks, targets and regulations. Tight supervision and incentives achieve quick results. This approach appeals to central level bureaucrats who aspire to reinterpret development problems into 'engineering' problems amenable to modern management techniques[46]. So the challenge becomes one of measuring 'needs' and thence specifying resources and supplies to be provided. This can then be easily mapped into corresponding budgets, targets, goals and plans. In this instance the 'need' is for women and children to receive treatment, detailed plans are drawn up to supply the various inputs such as drugs, training etc. by a centralized bureaucracy. This approach has been very successful in increasing the coverage of a number of interventions most vividly exemplified by the eradication of smallpox.

However these studies show the limitation of such an approach especially for an intervention such as PMTCT. This is because it is an example of a discretionary, transaction intensive intervention. Services are discretionary to the extent that their delivery requires decisions by providers to be made on the basis of information that is important but inherently imperfectly specified and incomplete, thereby rendering them unable to be mechanized. The example of making the correct decision with respect of infant feeding choices shows how each decision is context specific, is difficult to assess whether the correct decision has been made and hence it is very difficult to monitor whether or not the right decision was taken. The transaction intensiveness signifies the fact that PMTCT requires a large number of transactions, nearly

always involving some face-to-face contact. All of this means that the mechanization of the delivery of PMTCT will have limited effectiveness.

In applied economics the challenge of implementing such types of interventions are captured in the literature around the problem of Principal Agents. This problem arises whenever one actor called the principal (e.g. a firm) with one objective (e.g. profit maximization) contracts with another actor, called the agent (e.g., an employee), to undertake a task that affects the principal's objective function, knowing the agent may have a different objective function (e.g. leisure). In this case the problem facing the principal is how to structure the incentives for the agent so that the agent's best interest, given those incentives, leads to desirable outcomes for the principal. Even within a purely market organization there are principal–agent problems that deal with resources (what does the agent work with?), information (how does the principal observe agent effort and outcomes?), decision-making (which decisions are made by the agent, which by the principal?), delivery mechanisms (who does the agent interact with?), and accountability (how does the payoff to the agent depend on the agent's performance?). If we look at how PMTCT has been implemented thus far in all the study sites examined in this thesis (with the exception of the Paarl site)[47] then each of these aspects have been structured in a similar manner to that summarized by Pritchett and Woolcock in their analysis of failed development projects:

"Resources are centralized and canalized. The center collects nearly all resources from general taxes, rents, or aid……and then allocates them into budgets of line ministries. Information, if it exists at all, is tightly controlled and only flows internally and upward (not horizontally). Decision-making is done primarily by government agencies and their agents, with the discretion of local agents, at least on paper, tightly controlled by rules, regulations, and mandates from the top. Delivery mechanisms are via line agencies that reach directly from center to the service provider. Accountability of the service providers flows internally and upward, with accountability to the citizens occurring only via whatever political mechanisms exist for expressing discontent…." (Pritchett & Woolcock[48] p.197).

Botswana is a country that has scaled up PMTCT so that it now has achieved full national coverage. An essential aspect of this success has been the role of operational research and robust monitoring systems to inform managers and policy makers about bottlenecks in the system as well as to highlight the role of innovation and to hold them accountable (figure 4)

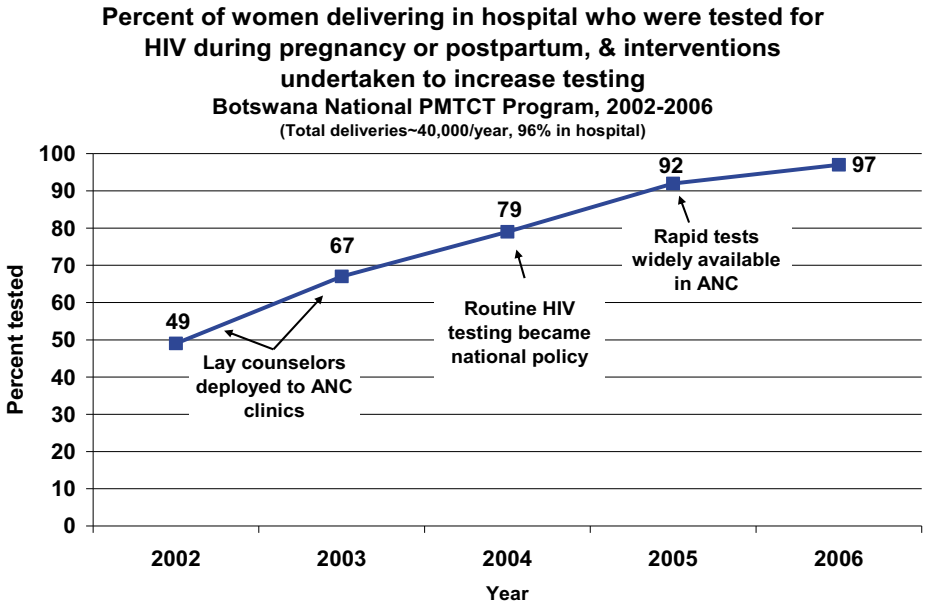
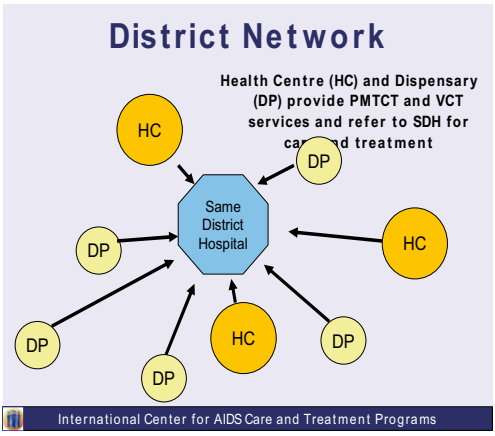


Figure 4. Percent of women delivering in hospital who were tested for HIV during pregnancy or postpartum. & interventions undertaken to increase testing

Underlying this impressive achievement has been the existence of a decentralised health system where district level managers are close enough to the population to tailor interventions accordingly. Another example comes from Tanzania that illustrates the importance of also planning the delivery points for scaled up PMTCT and paediatric ART services within the physical, human and financial constraints at the district level.

Dr Bazghina-werq Semo, 'PMTCT-Plus in Kilimanjaro', Tanzania. (taken from Chopra & Agabu[49])



The District Network approach in Tanzania uses health centres and dispensaries to provide VCT, PMTCT and referral services. This strategy decongests hospitals, strengthens PHC at the facility level and expands access to needed services. At the district level detailed planning has gone into how to integrate PMTCT interventions into MCH services. This is convenient, minimizes loss to follow-up and promotes the family-centred approach. Essential start-up activities include facility development, procurement and management of supplies, strengthening laboratory capacity, establishing links within and between sites, community mobilization, and monitoring and tracing systems. Status disclosure, client loss with referrals and denial are client-related challenges, while human resources and quality of care are system-related challenges.

This then needs to be accompanied by building the management capacity of district health teams in being able to perform programme planning, implementation, monitoring and evaluation and integrated supervision of quality improvement. Well functioning district teams have used the opportunity of integrating PMTCT into MCH to strengthen the institutional relationships. Through the process of using data to identify and solve problems together health workers and managers learn to address the blockages and barriers to cooperation and teamwork. It has been the overall aim of the body of work behind this thesis to provide district health teams with the concepts and tools to perform this task better.

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